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# Hans Selye and beyond: responses to stress

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> Only when we know what has been done by earlier contributors can we judge the present scene.
>
> The Way of the Investigator
> W. B. Cannon (1871–1945)

## INTRODUCTION

The stresses of modern life continue to be a popular topic within, as well as outside, the medical field. It is widely accepted that this hard to define entity is hurting us, if not killing us outright. Investigators, as well as victims, of cardiovascular disease, autoimmune disease, mental illness and even cancer have sought to place significant blame on this omnipresent nemesis *stress*. Violent human behaviors are on a dramatic upswing. Homicide, domestic violence, 'road rage' and even biological warfare are only a few of the contemporary manifestations of 'The Stress of Life'. The good (eustress) and bad (distress) effects of stress are not limited to individuals. They are presently molding global communities and stress response patterns at all levels of life. Global warming is stressful for myriad flora and fauna besides humans. Acid rain, smog, ozone and water pollution continue to make their steady contributions as global stressors and aggressors. How will we survive? Preventative and reparative strategies must be implemented at a global environmental level. Humans must devise methods to neutralize the ongoing production of noxious wastes henceforward. This challenge for the global community must be driven by statesmen and fueled by accurate scientific knowledge. As a practicing physician, I am in awe of the dimensions of this undertaking, which greatly exceed those of my own discipline. As a teacher and father, hope lies within my power to guide and inspire. Finally, as a clinician, I am responsible for managing the unwanted outcomes of an individual's response to 'The Stress of Life'. What then is stress? Dr Hans Selye devoted his career to the study of stress and summarized his extensive investigations addressing the question in this way: (stress is) 'a non-specific response of the body (cell, tissue, organ) to any demands ... stress, as life itself, is an abstraction having no independent existence of its own'. This characterization suffers from a certain vagueness that plagued Dr Selye and continues to cloud and hinder the development of the stress field today. There is a wealth of new knowledge characterizing the cellular response to stress (as evidenced by the need for this journal). The aim of this article is to acquaint the reader with Dr Hans Selye's work on the stress response and present clinical areas where the application of the stress response may prove fruitful in both understanding and treating complex, modern disease processes.

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### Budapest, Hungary, 1–5 July 1997, Stress of Life Congress

Approximately 1000 investigators from the world over were assembled by Dr Péter Csermely and colleagues to exchange their work and ideas on the response to stress, in recognition and honor of Dr Selye's 90th birthday (Fig. 1). The title of the meeting was borrowed from the title of Dr Selye's popular publication by the same name, *The Stress of Life*, a streamlined, autobiographical synopsis of Dr Selye's voluminous investigations into stress responses of all varieties (Selye 1976a). The quantity and variety of scientific stress-related information covered during this meeting was immense and served as clear testament that Dr Selye's legacy lives on. Investigators from all walks of


**Fig. 1** Logo of the International Congress of Stress, an interdisciplinary discussion commemmorating the 90th birth anniversary of Hans Selye. Circular pattern: decoration of an 1100-year-old Hungarian silver bag-plate found in Bezdéd, Hungary. Center: drawing of a Hungarian bow from the 9th century.

life and disciplines were represented, and reflected in themselves and their work, the truly universal nature of the response to stress as recognized by Dr Selye over 60 years ago. More importantly, this meeting provided a venue for the molecular and cellular biologists to directly interact with the more traditional stress enthusiasts. These groups were in turn showered with the colorful honorary presentations given by successful trainees of the late Dr Selye. An overview of this meeting is beyond the scope of this article. The plenary sessions will appear in a forthcoming publication (Csermely 1997).

## DR HANS SELYE (1907–1982)

Dr Selye was a clinical endocrinologist and experimental biologist who focused his efforts on an exhaustive study of the stress response. As with many great investigators, Dr Selye's initial work was both serendipitous and yet, because of his training and scientific rigor, predictable. While searching for a yet to be identified ovarian hormone, he recognized that the pathophysiologic responses he consistently observed in experimental animals receiving an injection of the ovarian extract were not ovary-specific but rather reflected a common response pattern of the intact animal which followed the administration of *any* foreign or noxious stimulus. Medical bias at the time was focused on the identification of organ or tissue specific phenomena such as the hormones of the hypothalamic-pituitary-adrenal axis (to which Dr Selye made significant contributions). Dr Selye's curiosity with the *non-specific* nature of this response and his recognition of its significance as a universal response to stress (noxious stimuli) represented a significant shift in thought at the time. This initial paradigm was succinctly delineated in a single page article in *Nature* (Selye 1936). His use of the words 'nocuous stimuli' was in place of the term stress which he had preferred to use, except that it had not yet been clearly defined nor was it generally accepted as a medical term at the time. The stress response occupied the center of Dr Selye's research efforts, leading eventually to the development of the concepts of the General Adaptation Syndrome (GAS) and the Diseases of Adaptation. A detailed dissertation of these concepts can be found in a number of Dr Selye's writings (Selye 1950, 1976b). A full length publication that appeared in the *Journal of Clinical Endocrinology* entitled 'The General Adaptation Syndrome and the Diseases of Adaptation' is an excellent place to rapidly review Dr Selye's principle theses (Selye 1946). Briefly, noxious stimuli are considered stressors and the organism's responses considered stress or the stress response. The stress response is divided into three overlapping temporal stages; Stage 1 – alarm reaction, Stage 2 – stage of resistance and Stage 3 – stage of exhaustion. All organisms will pass through each of these stages provided there is continued exposure to the stressor. A summary of Dr Selye's characterization of these stages of the stress response is depicted schematically (Fig. 2). The response to stress is triphasic. Remarkably, many contemporary scientists have independently described a similar pattern of resistance to noxious stimuli in cell biology, cancer biology, thermal biology and cardiovascular physiology. Some have even drawn curves similar to Figure 2 describing their respective models, while failing to recognize the relationship to either one-anothers' work (i.e. non-specificity) or to Dr Selye's. The outcome of an individual's exposure to noxious conditions depends greatly upon the timing of exposure relative to the development of a stress response. Current medical bias assumes a state of debility will follow injury. Clinicians continue to practice their art largely ignoring the temporal nature of an individual's response to stressors. During the response to stress there will be periods of sensitivity and resistance to stress which will be observed in a predictable fashion.

## STRESS LITERATURE AND WRITING

Dr Selye was a voracious reader and writer. He built an extensive library of stress-related literature and in so doing developed his own system of cataloging and of writing. His system of cataloging was an improvement over the Cutter and Dewey decimal systems, and as such, was published through five editions until the computer made it obsolete. Dr Selye's stress library is located and maintained at the University of Montreal, Quebec, Canada under the guidance of Professor Beatrice Tuchweber, President, Hans Selye Foundation. His writing is unique, thoughtful, and clearly an improvement over the style of scientific writing that continues to be used today. Dr Selye felt there were two competing issues that were placed at odds by modern scientific writing. On

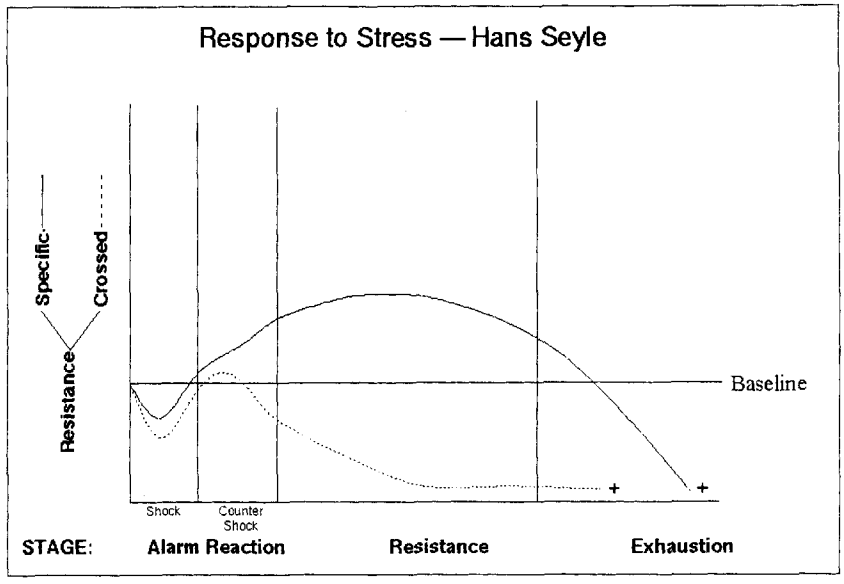


**Fig. 2** Schematic representation of the changes in specific (full line) and crossed (dotted line) resistance during the three stages of the General Adaptation Syndrome. The progress of time is indicated along the abscissa and the degrees of resistance along the ordinate. Reproduced with permission of the publishers from Perdrizet 1997 and adapted from Selye 1946.

the one-hand there is the objective analysis and presentation of scientific facts as they appear in the literature, and on the other, there is the subjective evaluation and synthesis of the particular author reporting on such literature. The first, which Dr Selye termed 'analysis', is simply the sterile compilation of facts in a catalogue format that is dry, diverse and represents the substantive component of his writing method. The analysis format is encyclopedic, lacking a creative component, and as such, would do little to further the development of scientific thought. The second portion, termed 'synthesis', is largely the subjective interpretation of the author permitted to 'free wheel'. The latter would allow the author's personal insights to guide the creative process and thereby take the current body of scientific knowledge to a higher level. This system is called 'analytico-synthetic style' and is described in 'Prefatory Remarks' in *Stress in Health and Disease* (Selye 1976b). Modern medical writing combines these two components into user-friendly prose and in so doing severely limits and cheapens the final product.

## MODERN MEDICINE AND STRESS CONDITIONING

A prevalent, iatrogenic modern malady to which nature has minimal intrinsic ability to adapt is the condition of *acute reoxygenation.* Living matter has gradually adapted to life in an oxidizing environment. Higher life forms, specifically mammals, are absolutely dependent on a minute-to-minute supply of reactive oxygen as a form of obligate toxin. Modern medicine has created many situations in which this life-sustaining element is acutely deprived and then rapidly restored to tissues and cells, such as during cardiovascular surgical procedures. The acute deprivation of oxygen is always poorly tolerated, save for when the simultaneous situations of accidental or medical hypothermia occurs. The protective effects of hypothermia are poorly understood but our current model can be largely attributed to Van't Hoff's insightful application of the Arrhenius equation to cellular metabolism (Popovic and Popovic 1974). Modern medicine has reaped the benefits conferred by hypothermia as first defined by the practice of cardiovascular surgery, over 40 years ago. Despite the ability to partially attenuate injury *during* oxygen deprivation, all tissues receive additional injury at the time of (and because of) the re-introduction of oxygen into cells that have been altered by ischemia. This reoxygenation injury was originally designated the 'oxygen paradox' and is now considered to be a major mechanism by which ischemia/reperfusion leads to cytodestruction; it detracts from the functional outcomes following many otherwise 'successful' medical interventions. There is pressing need to actively limit the tissue damage which results from acute ischemia/reperfusion events.

Despite the wide-reaching implications of the stress response as recognized by Dr Selye, I am puzzled by the lack of emphasis given to his work by educators in modern medical and biomedical sciences. Dr Selye cautioned that the term stress is abstract, and as such, is a difficult concept to define and thus permit close focus. Having carried out my own 'state-of-the-art' medical and

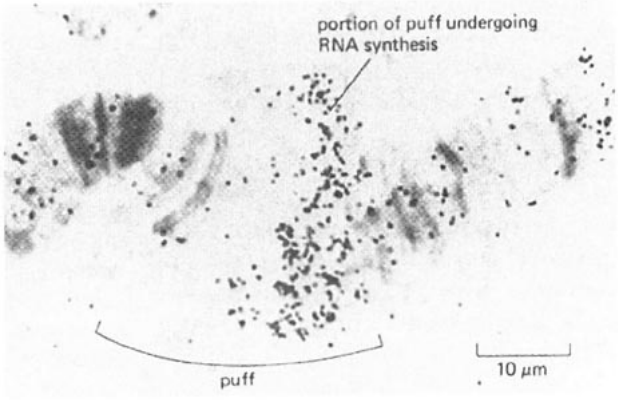


**Fig. 3** An autoradiogram of a *Drosophila* chromosomal puff undergoing RNA synthesis. Reproduced with kind permission from *Molecular Biology of the Cell*, first edition, with permission from Garland Publishing, Inc. and kindly provided by Jose Bonner.

scientific education between the years 1982 and 1992, I cannot recall ever receiving formal instruction regarding Dr Selye's work. Contemporary teachings focus on the works of Claude Bernard (1813–1878) and William Cannon (1871–1945), emphasizing the hypothalamic-pituitary-adrenal axis and the cardiorenal responses to stress. Yet no mention was made of the volumes of work reported by Dr Selye and summarized by the General Adaptation Syndrome.

During my graduate studies at the University of Chicago (1985–1989), I was introduced to the heat shock response (HSR), which I later learned was an example of a 'universal' adaptive response to stress at the cellular level. This cellular stress response had been initially described over 20 years previously by Ferruccio Ritossa (1962) without specific reference to Dr Selye's works in the context of environmentally-induced puffing of *Drosophila* polytene chromosomes (Fig. 3). Furthermore, the paucity of applications of the HSR to clinical medicine I also consider perplexing, as previously expressed by Dr J. German, a clinical hepatologist, over 12 years ago (German 1974). As a result of my training in general surgery, I was well versed in surgically-induced stresses to which patients are exposed on a regular basis. I began to investigate the potential clinical benefits offered by the acquired state of cytoprotection known to be associated with acute heat shock gene expression. The parallel phenomenon of thermotolerance, thermal preconditioning, which results in increased resistance to thermal injury, had been characterized since the 1970s and represented a *functional* model with which to study the state of stress-induced cytoprotection. The anticipated state of thermotolerance observed following exposure to thermal stress closely mimics Dr Selye's stages of the response to stress. The thermotolerance models provided the background to address the purposeful enhancement of resistance or tolerance to medically relevant, noxious conditions such as ischemia/reperfusion injury. Serendipitously, while searching the literature on stress responses, I stumbled upon Dr Selye's textbook *The Physiology and Pathology of Exposure to Stress* (Selye 1950). As a clinician, I could readily identify with his subject matter and as a scientist I could identify with his insight into nature's secrets. It readily became apparent that there exists marked parallels between Dr Selye's models and phenomena and the more recent observations being reported in the heat shock and hyperthermia literature. The non-specific response to diverse noxious stimuli resulted in a 'universal response' for both Dr Selye and heat shock/thermal biologists alike. Suddenly, Dr Selye's insight had been extended to the molecular level! Furthermore, these universal responses were associated with the transient acquisition of the ability to resist lethal insults. The resistance to *lethal* insults follows a prior exposure to *sublethal* stress and is consistently associated with the enhanced expression of the heat shock genes. Many investigators had observed a similar pattern of resistance to injury by prior exposure to sublethal noxious stressors including hyperthermia, sepsis, ischemia and toxin administration. Oftentimes investigators observed protection following exposure to noxious stimuli and labeled it 'paradoxical', relative to the anticipated state of debility or sensitivity which they expected to observe. These phenomena of resistance to injury and death were examples of Dr Selye's second stage of the stress response.

By inducing the heat shock response with whole-body hyperthermia (42.5°C × 15 min) and recovery (37°C × 8 h) in rodent kidney donors, I hypothesized that transplanted organs would resist injury from cold ischemia and reperfusion. The resistance to injury that develops following heat shock gene expression could be used as a method to achieve stress-injury prevention in clinical situations in which injurious events were anticipated. The purposeful induction of the stress response and its associated state of stress resistance prior to exposure to a potentially lethal stressor was termed 'stress conditioning'(Perdrizet et al 1989). The acquired state of transient stress protection is termed the 'protected phenotype' (Perdrizet 1997). Stress conditioning would allow for the purposeful induction of the protected phenotype (HSR, thermotolerance, Stage 2 of GAS) prior to medical/surgical procedures in which there is risk of cell and tissue damage. This approach might be considered a form of preventative medicine practiced at the cellular and molecular levels. My work and interests unknowingly had focused upon the second stage of the response to stress as delineated by Dr Selye. Reading his works significantly reinforced the theory and practice of stress conditioning. Stress conditioning is any process that purposefully places a cell, tissue, organ or organism into the second stage of the stress response, the stage of resistance (cytoprotection, protected phenotype).

Interestingly expression of Hsp70 is a consistent biomarker for this state of acquired cytoprotection or stage of resistance. Numerous experimental models have confirmed that heat shock and recovery of mammalian tissues results in a transient state of cytoprotection against ischemia/reperfusion injury (Perdrizet 1997). Protection can be both specific and non-specific to the sublethal conditioning stress. Thus, heat shock can confer specific protection (e.g. thermotolerance) as well as non-specific or cross protection against sepsis, cellular toxins such as heavy metals or ethanol, and ischemia/reperfusion. I suspect the ability to acquire the 'protected phenotype' will be as universal as the heat shock response and Dr Selye's stress response.

## CURRENT CLINICAL CHALLENGES

The field of trauma surgery is currently defining a new approach to the emergent care of the severely injured patient. Severely injured patients who require extensive operative therapy frequently expire intraoperatively secondary to 'metabolic failure or exhaustion' (Morris et al 1996). This state is characterized by severe and irreversible acidosis, hypothermia and coagulopathy and is uniformly lethal. Recently, it was recognized that this subset of severely ill patients, if identified early, would have a better outcome if their operative therapy was divided up into several stages. The first stage has been termed 'damage control laparotomy' and is the initial, emergent operation performed to stop life-threatening hemorrhage and gastrointestinal leakage. Once this is accomplished, the patient is transported from the operating room to the intensive care unit where intensive therapy is directed at metabolic support to restore normal homeostasis and allow for a period of recovery. The second stage involves a return visit to the operating room, at which time definitive repairs and reconstruction can be carried out in a now stable patient. The period between operations varies but is generally 48 h. By managing patients in a staged fashion, the patient survival has increased from 0–20% to greater than 50%. It would appear that through a process of trial and error the surgical community has unknowingly taken advantage of the patient's intrinsic adaptive response and has allowed the patient time to move from Stage 1 of Dr Selye's stress response into Stage 2 and is thus more resistant to the stressors related to the reconstructive phase of surgical therapy. I suspect the metabolic basis for the successes of damage control laparotomy is at the cellular level and is analogous to the cytoprotection observed to follow heat shock gene expression in previously reported models of stress conditioning. The initial shock, trauma and operative intervention followed by a period of normal homeostatic recovery has in essence 'stress-conditioned' the patient.

Dr Selye summarized the clinical manifestations of stress into one word: *inflammation.* Such a designation is an over-simplification, but is as illustrative today as it was 60 years ago. Inflammation is consistently blamed as the fundamental underlying pathologic process in diverse disease processes; autoimmune, infectious, cerebrovascular, cardiovascular and even diabetes. The systemic inflammatory response syndrome (SIRS), as seen in medical intensive care units, is the harbinger of the leading, untreatable cause of death in modern intensive care units throughout the world, the multiple organ dysfunction syndrome (MODS) (Demling et al 1993). Inflammation (stress) continues to contribute to the morbidity and mortality of critically ill patients despite their receiving the most technologically advanced care possible. Clearly, modern medical technology has, through its successes (artificial life support systems), created acute and subacute stressful conditions never before experienced by complex life forms. Currently, there is no effective therapy for patients responding to severe, overwhelming stressors. Furthermore, there is very little understanding as to the pathogenesis of these (mal)adaptive responses at the cellular level. Certainly the cellular stress response is involved and when activated chronically instead of transiently may even be contributing to a modern version of Dr Selye's Diseases of Adaptation. Just as modern society has progressed to create new stresses to challenge biological adaptation, so too within modern medicine. Running parallel with these 'new' maladies is the development of new knowledge in environmental and medical sciences and in molecular biology in particular. It appears, however, that new knowledge will always lag behind our ability to create needs for it.

## SUMMARY

All cells have conserved similar adaptive responses to potentially lethal noxious conditions. The response to persistent stress is time dependent and triphasic. Dr Selye clearly described these phenomena on a clinical level and in experimental animal models, modern molecular (heat shock) and cellular (thermal) biologists have provided us with relevant molecular correlates. The challenges remain to integrate the new knowledge without loosing sight of the old, and in the end achieve a better understanding of current medical therapies. A bid to all, read and re-read the works of Dr Hans Selye.

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